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Metacarpophalangeal Pattern Profile Analysis in Noonan Syndrome

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Metacarpophalangeal pattern (MCPP) analysis is an application of an anthropometric technique that provides a quantitative assessment of the amount and direction of abnormality in the hand skeleton. MCPP analysis was undertaken on 15 individuals (9 males, 6 females) with Noonan syndrome ranging in age from 0.1 to 36 years with a mean age at 11.6 years. The overall average Z score for the MCPP variables was –2.1 and the range was –2.5 (for metacarpal two) and –1.5 (for middle phalanx 5). The average hand pattern variability index, a measure of hand bone length relationships, was abnormal. A Pearsonian correlation analysis was used to assess similarity between the mean pattern and each of the 15 individual patterns. Nine (60%) of the fifteen individuals with Noonan syndrome had significant positive correlations ($P < 0.05$), indicating homogeneity or similarity in the hand patterns. A stepwise discriminant analysis was performed on Z score data from the individual hand bone measurements on the 15 subjects with Noonan syndrome and 41 healthy controls (24 females, 17 males; mean age = 13.1 years with age range of 9.6 to 18 years). This analysis produced a discriminant function with two MCPP variables (metacarpal 1 and middle phalanx 3) entering into the function and producing a correct classification rate of 93%. The two MCPP variables contributed to the overall difference between individuals with Noonan syndrome and the normative sample. The hand pattern variability index was outside of the normal range, indicating an abnormal MCPP with multivariate analysis. The MCPP analysis may be useful as a tool for diagnosis in screening subjects for Noonan syndrome. Am. J. Med. Genet. 92:128–131, 2000. © 2000 Wiley-Liss, Inc.

KEY WORDS: Noonan syndrome; metacarpophalangeal pattern profile (MCPP); pattern variability index; discriminant analysis; correlation studies

INTRODUCTION

Noonan syndrome is a well-recognized condition of neck webbing, pectus excavatum, cryptorchidism, pulmonic stenosis, low posterior hairline, short stature, and a particular facial appearance [Noonan and Ehmke, 1963]. It is inherited as an autosomal dominant condition. Owing to phenotypic variability, early recognition of Noonan syndrome individuals may be difficult. Therefore, quantitative methods based on radiographic measurements may be helpful in the identification of individuals with Noonan syndrome with or without a positive family history.

Metacarpophalangeal pattern profile (MCPP) analysis is an evaluation of the hand skeleton based on a comparison of the 19 tubular bone lengths to normal bone length standards as described by Poznanski et al. [1972] and Garn et al. [1972]. This method provides a quantitative assessment of the amount and direction of abnormality of the hand skeleton. MCPP analysis has been used to evaluate numerous syndromes [Butler et al., 1982, 1985, 1986, 1987a,b, 1988a,b,c, 1993; Poznanski, 1984; Butler and Meaney, 1985; Burns et al., 1993]. Recently, we applied a method of MCPP analysis on 15 individuals with Noonan syndrome to evaluate its potential as a screening tool to identify individuals at risk for Noonan syndrome.

MATERIALS AND METHODS

Posterior-anterior hand radiographs (Fig. 1) were obtained on both hands of 15 individuals diagnosed with

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Fig. 1. A typical hand radiograph from an 11-year-old male with Noonan syndrome.

Noonan syndrome. The diagnosis was made by more than one clinical geneticist in documenting the presence of prominent features in this syndrome, including a particular facial appearance, short stature, skeletal findings, congenital heart defects, and genital problems [Jones, 1997]. The group included nine males and six females ranging in age from 0.1 to 36 years with a mean age of 11.6 years. All individuals were Caucasian and unrelated. The metacarpophalangeal bone lengths of each patient were measured to the nearest millimeter with a vernier caliper and compared to bone length standards (appropriate for age and sex) published by Garn et al. [1972] (white Americans, age 2 years to adult) and Poznanski [1974] (Gefferth Hungarian sample, birth to 15 months). Through these comparisons, Z score values for the 19 bones for each patient were obtained (Z score = observed bone length minus mean bone length divided by standard deviation). Therefore, the MCPP on a given patient is a set of 19 Z scores, which may be plotted on a graph or subjected to various statistical procedures for study and comparison with the MCPP of other patients or groups of patients. A pattern variability index $[\Sigma Z^2/N - (\Sigma Z/N)^2]$ for quantitation of hand changes described by Garn et al. [1987] was calculated from the MCPP data of our patients.

Correlation Studies

We derived a mean pattern profile from the 15 patients based on the average Z score for each bone (Fig. 2). The pattern from each patient was compared to the group mean pattern using Pearsonian correlation coefficients.

Discriminant Analysis

A stepwise discriminant analysis was performed on the 15 subjects with Noonan syndrome and 41 healthy controls (24 females, 17 males; mean age = 13.1 years with an age range of 9.6 to 18 years). A forward stepwise method of discriminant analysis [Norusis, 1988] was performed on the 19 Z score variables and age for the individuals in our study (Fig. 3).

RESULTS

The mean Z score of the 15 patients with Noonan syndrome fell between −2.5 (for metacarpal two) and −1.5 (for middle phalanx 5). The overall average Z score for the MCPP variables in our subjects with Noonan syndrome was −2.1. Only five of the nineteen hand bones from our 15 subjects had an average Z score within the normal range, i.e., between +2 and −2. The mean pattern profile based on our 15 subjects showed up and down deviation with the largest Z score value of −1.5 for middle phalanx 5. Next, a Pearsonian correlation program was used to assess similarity between the mean pattern in each of the 15 individual patterns. Nine (60%) of fifteen individuals with Noonan syndrome had significant positive correlations ($P < 0.05$) (see Table I).

A forward stepwise discriminant analysis was performed on the 15 subjects with Noonan syndrome and 41 healthy controls (24 females, 17 males; mean age = 13.1 years with age range of 9.6 to 18 years). This analysis produced a discriminant function with two MCPP variables (metacarpal 1 and middle phalanx 3) entering into the function and resulted in a correct classification rate of 93%. The hand pattern variability index, a measure of hand bone length relationships [Garn et al., 1987], was calculated on each Noonan syndrome subject. The average index score was 1.0. A score above 0.7 is considered abnormal.

DISCUSSION

Six of the nineteen hand bone averages were within normal range (+2 to −2 Z scores), whereas the remaining 13 bones were outside of the normal range. Four of the six bones that were within the normal range included distal phalanges 1, 2, 3, and 4 as represented by the MCPP (Fig. 2). Only distal phalanx 5 was outside the normal range. All of the metacarpals and proximal phalanges were short and outside of the normal range. The hand pattern showed up and down deviation and the calculated hand pattern variability index was outside of the normal range in this syndrome. Most subjects had significantly positive individual MCPP correlations with the Z score group mean indicating homogeneity or similarity in the hand patterns among our Noonan syndrome subjects. Six (40%) individuals in our study showed no significant correlation with the mean pattern profile. The average age of those individuals whose patterns did not correlate with the av-

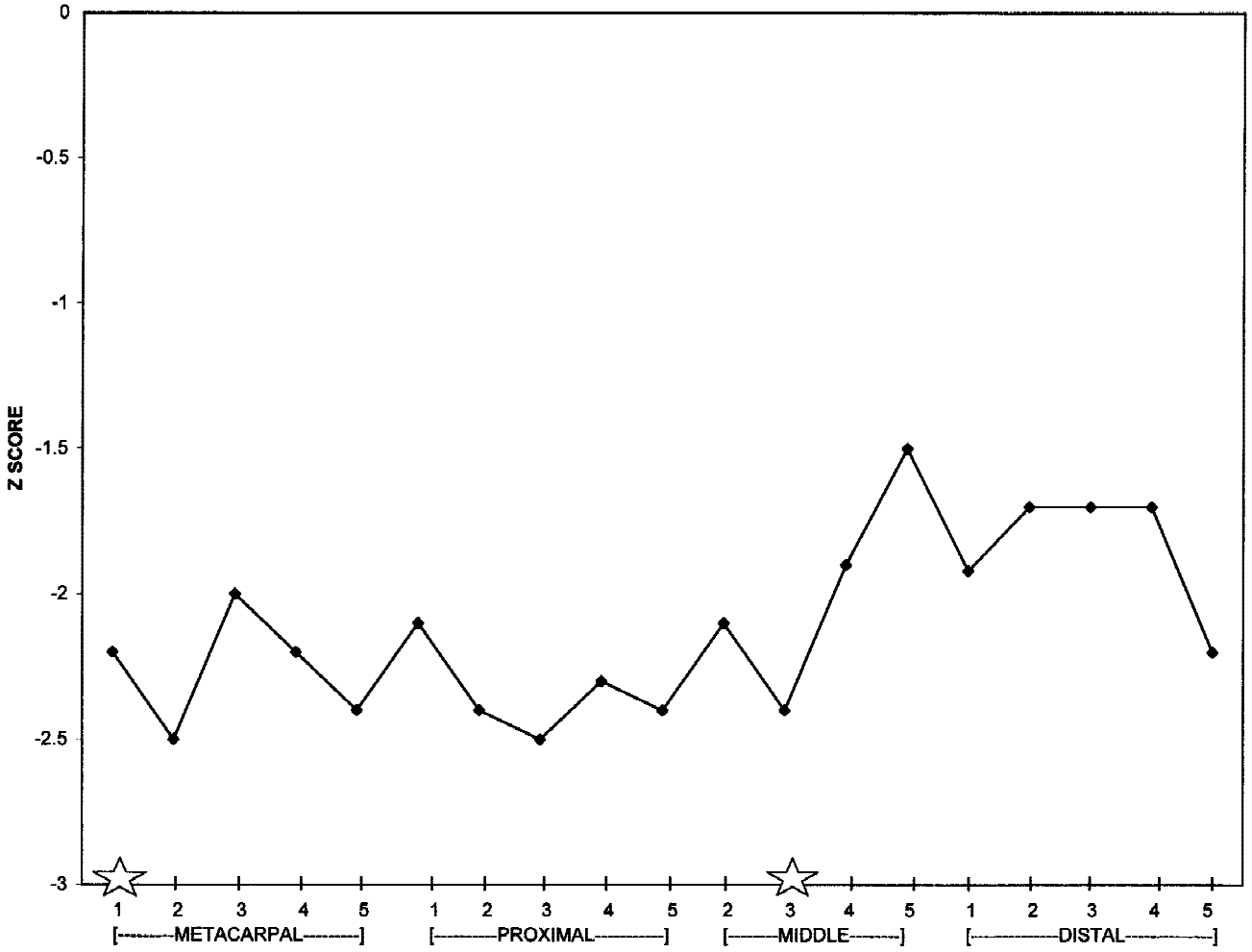

Fig. 2. Mean MCPP on 15 individuals with Noonan syndrome. Star indicates the bone that was selected in the discriminant analysis.

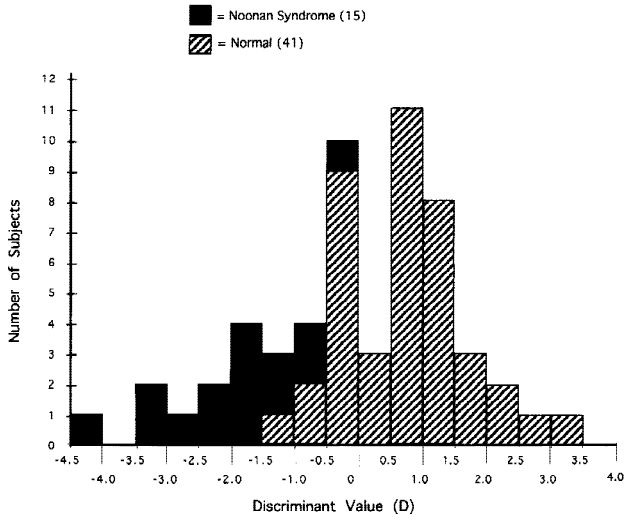

Fig. 3. Histogram depicting normal and Noonan syndrome classification by discriminant analysis. D = 0.69 + 0.49 (Z score of metacarpal 1) + 0.63 (Z score of middle phalanx 3).

TABLE I. Correlations Between Individual and Group Mean MCPP, Average Z Scores and Pattern Variability Indices in Noonan Syndrome

Age (years)	Sex	Average Z score	Pattern variability index[a]	Correlation
8.3	F	−2.1	0.3	0.53*
10.0	F	−1.9	0.7	0.76***
12.5	F	−0.7	0.4	0.72***
13.5	F	−1.5	0.3	−0.35
24	F	−1.2	1.2	0.25
26.8	F	−2.3	0.1	0.02
0.1	M	−1.4	0.6	0.58**
1.4	M	−1.3	0.7	−0.14
1.8	M	−4.8	3.3	0.75***
5.6	M	−2.4	3.6	0.44*
6.1	M	−2.9	1.2	0.20
6.1	M	−2.2	0.6	0.71***
11.0	M	−2.9	0.3	0.83***
11.6	M	−2.6	0.7	0.70***
36.0	M	−1.5	0.6	−0.20

[a]Pattern variability index $[\Sigma Z^2/N - (\Sigma Z/N)^2]$ (an index above 0.70 is considered abnormal).
*$P < 0.05$ for one-tailed test.
**$P < 0.01$ for one-tailed test.
***$P < 0.0005$ for one-tailed test.

erage pattern was 18.0 years, whereas the average age of individuals with a significant correlation was 7.4 years, indicating possible hand pattern changes with age. Pattern heterogeneity has been reported in other conditions (e.g., Sotos syndrome, Butler et al., 1988b).

The discriminant analysis suggests effective delineation of Noonan syndrome patients with a correct classification of 93% based on two MCPP variables (metacarpal 1 and middle phalanx 3). Additional studies with larger sample sizes are needed to test the power of the discriminant function in distinguishing patients with Noonan syndrome from normal subjects and from patients with other conditions. In summary, our observations presented in this report suggest the potential of MCPP analysis as a diagnostic tool in screening subjects for Noonan syndrome.

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REFERENCES

Burns MA, McLeod DR, Linton LR, Butler MG. 1993. Metacarpophalangeal pattern profile analysis in Williams syndrome. Am J Med Genet 47:471–474.

Butler MG, Kaler SG, Yu PL, Meaney FJ. 1982. Metacarpophalangeal pattern profile analysis in Prader-Willi syndrome. Clin Genet 22:315–320.

Butler MG, Meaney FJ, Kittur S, Hersh JH, Hornstein L. 1985. Metacarpophalangeal pattern profile analysis in Sotos syndrome. Am J Med Genet 20:625–629.

Butler MG, Meaney FJ. 1985. Metacarpophalangeal pattern profile analysis in Prader-Willi syndrome: a follow-up report on 38 cases. Clin Genet 28:27–30.

Butler MG, Meaney FJ, Kaler SG. 1986. Metacarpophalangeal pattern profile analysis in clinical genetics: an applied anthropometric method. Am J Phys Anthropol 70:195–201.

Butler MG, Gale DD, Meaney FJ, Wadlington WB, Robinow M. 1987a. Metacarpophalangeal pattern profile analysis in Robinow syndrome. Am J Med Genet 27:219–233.

Butler MG, Gale DD, Meaney FJ. 1987b. Metacarpophalangeal pattern profile analysis in diastrophic dysplasia. Am J Med Genet 28:658–689.

Butler MG, Rames LJ, Wadlington WB. 1988a. Acrodysostosis: report of a 13 year old male with review of literature and metacarpophalangeal pattern profile analysis. Am J Med Genet 30:971–980.

Butler MG, Dijkstra PF, Meaney FJ, Gale DD. 1988b. Metacarpophalangeal pattern profile analysis in Sotos syndrome: a follow-up report on 34 subjects. Am J Med Genet 29:143–147.

Butler MG, Fletcher M, Gale DD, Meaney FJ, McLeod DR, Fagan J, Carpenter NJ. 1988c. Metacarpophalangeal pattern profile analysis in fragile X syndrome. Am J Med Genet 31:767–773.

Butler MG, Dahir GA, Gale DD, Meaney FJ. 1993. Metacarpophalangeal pattern profile analysis in de Lange syndrome. Am J Med Genet 47: 1003–1005.

Garn SM, Herztog KP, Poznanski AK, Nagy JM. 1972. Metacarpophalangeal length in the evaluation of skeletal malformation. Radiology 105: 375–381.

Garn SM, Leonard WR, Poznanski AK. 1987. Applications of the pattern variability index (OZ) to the quantification of dysmorphogenesis in the hand. Am J Med Genet 27:143–152.

Jones KL. 1997. Smith's recognizable patterns of human malformation. Philadelphia: W.B. Saunders. p 122–123.

Noonan JA, Ehmke DA. 1963. Associated noncardiac malformations in children with congenital heart disease. J Pediatr 63:469.

Norusis MJ/SPSS, Inc. 1988. SPSS/PC+ advanced statistics V2.0 for the IBM PC/XT/AT and PS/2. Chicago: SPSS, Inc.

Poznanski AK. 1974. The hand in radiological diagnosis, first edition. Philadelphia: W.B. Saunders.

Poznanski AK. 1984. The hand in radiological diagnosis, second edition. Philadelphia: W.B. Saunders.

Poznanski AK, Garn SM, Nagy JM, Gall JC. 1972. Metacarpophalangeal pattern profiles in the evaluation of skeletal malformations. Radiology 104:1–11.